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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/646,135	09/08/2000	Kazuko Hirabayashi	44342.011800	2368

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	4

DATE MAILED: 07/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/646,135	HIRABAYASHI ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-3 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 08 September 2000 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 1-3 are pending examination.

Election/Restriction

During a telephone conversation with Eugene Rzucidlo on 6/14/02 a provisional election was made with traverse to prosecute the species poly I: C. Thus, the species comprising mismatched poly I: C, poly A: U, and mismatched poly A: U in claims 1-3 are considered withdrawn from further examination. Applicant in replying to this Office action must make affirmation of this election.

Applicants' traversal is not found persuasive because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement. Therefore, species mismatched poly I: C, polyA: U, and mismatched poly A: U in claims 1-3 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected species, there being no allowable generic or linking claim.

The International Preliminary Examination Report for PCT/JP99/01438 is acknowledged.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on 3/24/98.

Specification

The specification contains misspelling of the word 'than' on page 12. These and any other, spelling errors should be corrected in response to this office action. Applicant is encouraged to review the specification for additional spelling errors.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A therapeutic agent comprising a complex comprising a cationic liposome with a double stranded RNA, which is poly (I): poly(C) and has a mean chain length within the range of 100 to 500 bp; 2) A therapeutic agent comprising a complex comprising a drug carrier consisting essentially of 2-O-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglcerol and a phospholipid with a double stranded RNA, which is poly (I):poly(C) and has a mean chain length within the range of 100 to 500 bp, and does not reasonably provide enablement for the full scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed invention encompasses making and/or using a complex comprising a cationic liposome with a double-stranded RNA for treating or preventing hepatitis in a mammal. The field of the invention lies in the producing complexes comprising a cationic liposome with a

double-stranded RNA and preventing or treating hepatitis in a mammal using the complex set forth above. It appears from applicants' disclosure, that the sole use of the complex is for in vivo method of treating or preventing hepatitis. The field of the invention lies in *in vivo* nucleic acid therapy.

Furthermore, and with respect to claims directed to any vector useful for nucleic therapy and directed to any treatment of a mammal; the state of the art in 1998, exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any nucleic acid therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several

major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

In addition, the state of the art teaches that hepatitis is a disease that is virally induced and includes hepatitis A, B, C, and other forms.

The state of the art teaches that poly (I): poly(C) is an anionic polymer that does not easily cross the cell membrane (Hirabayashi et al. Cancer Research, Vol. 59, pp. 4325-4333, 1999). Furthermore, previous research on dsRNA has focused almost entirely on their IFN-inducing activity and Poly(I):Poly(C) has an anti-proliferative effect against many tumor cells in mice (page 4325).

The as-filed specification provides working examples (pages 8-15), which are briefly described herein: Examples 1-9 teaches the production of a complex comprising poly (I): poly C and a cationic liposome and a phospholipid. Example 10 teaches the induction of in normal mouse's liver using i.v. injection of the complex produced in example 4.

The claimed invention is enabled for producing a therapeutic agent comprising a complex comprising a cationic liposome with a double stranded RNA, which is poly (I): poly(C) and has a mean chain length within the range of 100 to 500 bp and using the agent to induce interferon level in an animal to reduce hepatitis in a mammal by intravenously administering the complex to the mammal. However, the claimed invention is not enabled for the full scope of the claimed invention because the as-filed specification lacks sufficient guidance for one skilled in the art to use an agent for preventing (partial/complete protection) hepatitis in a mammal. In view of art of record teaching the unpredictability of determining which mammal is susceptible to hepatitis, the as-filed specification fails to provide sufficient guidance for how the working examples comprising inducing interferon expression in normal healthy mouse reasonably correlate to a preventive agent set forth in the claimed invention. The state of the art teaches that interferons have been used to manage hepatitis in mammals (Zein, 'Interferons in the management of viral hepatitis', Cytokines Cell Mol. Ther., Vol. 4, 1998, (abstract) Medline [online], Bethesda, MD USA: United States National Library of Medicine [retrieved on 7/11/02]).

> IFN treatment is not currently available for the acute hepatitis B, but has proven beneficial in chronic hepatitis B. It has become clear during the last two decades that IFNs have beneficial effects for patients with viral hepatitis B or C. Much more effort is needed to establish the optimal dose or duration of therapy. Studies addressing the pharmacokinetics of IFNs in patients with viral hepatitis are needed and methods to improve the bioavailability of these products to affected tissues such as liver may improve efficacy.

Furthermore, the art of record as exemplified by Ferrell (Pathology, Vol. 13, pg. 679 and pages 684-701, 2000) teaches that making the histologic diagnosis of hepatitis is usually an easy task, but not always. Many times, the cause of fibrotic or inflammatory process in the liver can be difficult to recognize because the liver responds to a wide range of injuries in only a limited number of ways. In view of the art of record and the lack of guidance provided by the specification for how to determine which mammals are susceptible to hepatitis and how to administer a preventive agent comprising a double stranded RNA to stimulate interferon level in the mammal to prevent hepatitis in view of the unpredictability of nucleic acid therapy, it would take one skilled in the art an undue amount of experimentation to reasonably correlate inducing interferon expression in a normal mouse to preventing hepatitis in any mammal.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed agents generate a preventive effect, how is it apparent as to how one skilled in the art, without any undue experimentation, use any agent as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record for preventing hepatitis in a mammal.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the for 1-2 listed above. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a nucleic acid therapy effect (preventing encompassing partial and/or complete protection) produced by any agent cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order

to practice the claimed invention based on the applicant's disclosure and the unpredictability of nucleic acid therapy.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The claims are directed to agents and pharmaceutical composition for treating or preventing hepatitis. The intended use of a product, in the instant claims for both agents does not

have patentable weight for prior art rejections. An intended use does not provide an alteration to the agent that distinguishes it from that taught in the art of record.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yano et al. (US Patent No. 5,298,614) in view of either applicants' own admission that there are known pharmaceutical or drug carriers including cationic liposomes, 2-O-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglcerol and a phospholipid in WO94/19314 (page 2 of the specification) or WO 94/18987. Yano teaches the poly I: poly C is a substance having a significant activity such as interferon induction action, proliferating inhibiting action for tumor cells in cancer-bearing mammalians and an immune system activating in vivo have been known (column 3, lines 32-40). Yano further teaches that when the chain length is limited to certain ranges, the resulting substance exhibit desired physiological activity with markedly less toxicity (column 4, lines 31-39). In addition, Yano teaches that experimental techniques have been developed for more accurately determining the molecular weight of macromolecular substances using gel electrophoresis (columns 8 line 61- column 9, line 15). Yano teaches that the fact that the control of molecular size of nucleic acid polymer within a specified range is the primarily important factor for remarkable reduction of toxicity of poly I: poly C and the preferred molecular size for using poly I: poly C is from 100 to 600 base numbers (column 11, lines 13-34). However, Yano does not specifically teach

an agent comprising a complex comprising a drug carrier consisting essentially of 2-O-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglcerol and a phospholipid with a double stranded RNA, which is poly (I):poly(C) and has a mean chain length within the range of 100 to 500 bp.

However, at the time the invention was filed, 2-O-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglcerol and a phospholipid were known in the art for delivering a single stranded nucleic acid copolymer (poly(A):poly(U)) and providing the composition for reducing tumors in a subject (WO 94/18987, abstract).

At the time the invention was made it would have been *prima facie* obvious for a person of ordinary skill, as a matter of obvious design choice to combine the teaching of Yano in view of applicants' own admission or WO 94/18987 to use 2-O-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglcerol and a phospholipid with a double stranded RNA, poly (I):poly(C) having a mean chain length within the range of 100 to 500 bp. One of ordinary skill in the art would have been motivated to use the cationic lipid with the agent for inducing interferon production in a mammal because cationic liposomes improve the stability of the double stranded RNA in cells of a mammal.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
7/14/02

DAVE T. NGUYEN
PRIMARY EXAMINER